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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SPIEGLER, ALEXANDER H

ART UNIT	PAPER NUMBER
1637	7

DATE MAILED: 11/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/826,522	Applicant(s) DEPHILLIPO ET AL.	
	Examiner Alexander H. Spiegler	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,39,40 and 58-94* is/are pending in the application.

4a) Of the above claim(s) *1 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39 and 58-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II (claim 39 and newly added claims 58-94) in Paper No. 6, filed on November 1, 2002 is acknowledged. Claims 1 and 40 have been withdrawn from consideration as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 39 and 58-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 39 and 58-94 are indefinite over "genes which encode a protein that indirectly affects oxidative stress" because it is not clear as to how a gene "indirectly" affects oxidative stress, how the gene "affects" oxidative stress, and furthermore, this recitation is not defined in the specification. Furthermore, the specification does not provide any examples as to what genes are encompassed by above recitation.

B) Claims 39 and 58-94 are indefinite over "genes which encode a protein which the level of expression of the protein is associated oxidative stress" because it is not clear as to how or what level of the expression of the protein is "associated" with oxidative stress. The specification does not define what levels of expression can be consider to be "associated" with

oxidative stress, and does not provide any examples as to what genes are encompassed by above recitation.

C) Claims 39 and 58-94 are indefinite over "the composition" and "the polymorphisms" because these claims lack antecedent basis. This rejection should be overcome amending the claims to recite, "the **anti-oxidant** composition" and "the **disorder-associated** polymorphisms.

D) Claims 39 and 58-94 over "assessing occurrence in the human's genome of disorder-associated polymorphisms" because it is not clear what a "human's genome of disorder-associated polymorphisms" actually is or comprises.

E) Claims 62-69 are indefinite over "the genes" because it is not clear as to what genes are being referred to, since it is not clear whether the genes listed from i) to xxvii) are genes from a), b), c), d), or e) or all of the above or some of the above, etc.

F) Claims 70-81 over "higher stringency" because it is not clear as to how an oligonucleotide anneals with "higher stringency". Furthermore, it is not clear as to how an oligonucleotide simply "anneals" with **the** disorder-associated polymorphism.

1st Paragraph (Written Description)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 39 and 58-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

35 U.S.C.§ 112, requires, *inter alia*, that a patent specification contain a written description of the invention and the manner and process of making and using it "...in such full clear and concise terms as to enable one skilled in the art... to make and use" the invention. While it is well settled that a patent application need not teach each possible embodiment of the claimed invention, it is manifestly true that written description cannot be settled by reliance on that which has not been achieved in the art, or that which is not disclosed in the specification. That is, a specification is not considered to satisfy the requirement for an adequate written description if it fails to disclose the specific starting materials or conditions for making the invention. (*Genentech, Inc. v. Novo Nordisk*, 108 F3d. 1361, 42 USPQ2d 100. Fed. Cir. 1997), or evidence that the applicants at the time the application was filed, has possession of the claimed invention.

Additionally, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed* (See page 1117)." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (See Vas-Cath at page 1116)."

The claims are drawn to methods of selecting a dose of an anti-oxidant composition for administration to a human, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least two genes selected from the group consisting of,

a) genes which encode an enzyme that catalyzes conversion of a toxic oxygen species to a less toxic oxygen species;

b) genes which encode a protein that provides protection against oxidative stress;

c) genes which encode a protein that induces production of a toxic oxygen species;

d) genes which encode a protein that indirectly affects oxidative stress; and

e) genes which encode a protein which the level of expression of the protein is associated oxidative stress, whereby the occurrence of any of the polymorphisms is an indication that a greater dose of the composition should be administered to the human; and selecting a dose of the composition based on occurrence of the polymorphisms.

The specification teaches several isolated polymorphisms in specific genes, which can be informative for susceptibility to oxidative stress (pg. 12-13). Specifically, the specification teaches two polymorphisms in MnSOD, two polymorphisms in CZSOD, and one polymorphism in each of thirteen distinct, unrelated genes. Therefore, the specification teaches only two polymorphisms in two distinct genes, and one polymorphism in thirteen unrelated genes.

The claims lack written description for reasons:

1) Genes a) through e) are each drawn to a specific genus of genes, the specification only teaches species of each these genes, which are not a representative number of species for support of the claimed genus. For example, "genes which encode a protein that indirectly affects oxidative stress" would encompass an extremely large number of possible genes that could be encompassed by this genus. The specification does not provide any guidance or description as to what genes are encompassed by this genus, let alone, any evidence that Applicants were in possession of any of these genes. In other words, Applicants have not adequately described genes that are encompassed in a) to e).

2) The claims are drawn to assessing occurrence in any disorder-associated polymorphisms, but the specification has only taught isolated polymorphisms in distinct genes. The specification teaches: a "disorder-associated polymorphism is an alternative form of a portion of a gene, wherein occurrence of the alternative form in the genome of a human has been correlated with exhibition by the human of a disease or a pathological state" (pg. 7, ln. 15-17). Therefore, a "disorder-associated" encompasses a large number of possible polymorphisms. The claims are drawn to occurrence of any polymorphism that "is an alternative form of a portion of a gene, wherein occurrence of the alternative form in the genome of a human has been correlated with exhibition by the human of a disease or a pathological state", however, the claims only teach one or two polymorphisms in each gene. These one or two polymorphisms are not representative of the unlimited number of polymorphisms in genes a) to e) that is claimed. Furthermore, Applicants were only in possession of the polymorphisms on page 12 of the specification, and were not in possession of the plurality of possible polymorphisms that are encompassed by the claims.

Therefore, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus, the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

1st Paragraph (Enablement)

6. Claims 39 and 58-94 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In Ex parte Forman, 230 USPQ 546 (Bd. App. 1986), the Board considered the issue of enablement in molecular biology. In considering these factors:

1) In order to practice the invention, the practitioner must find the possible genes that satisfy the requirements of the genes set out in claim 39, and furthermore, a practitioner must find polymorphisms in these genes that affect oxidative stress. The specification does not list or suggest what genes would fall into each category of genes listed in a) through e), and it could conceivably encompass hundreds, if not, thousands of genes, especially in light of claim language such as, "genes which encode a protein that **indirectly** affects oxidative stress".

Claims 62 and 87 list a number of genes, however, the specification does not teach under what categories these genes fall under, and only teach one or two polymorphisms in each gene that may be associated with oxidative stress.

2) The specification provides guidance on several isolated polymorphisms in specific genes, which can be informative for susceptibility to oxidative stress (pg. 12-13). Specifically, the specification teaches two polymorphisms in MnSOD, two polymorphisms in CZSOD, and one polymorphism in each of thirteen distinct, unrelated genes. Therefore, the specification teaches only two polymorphisms in two distinct genes, and one polymorphism in thirteen unrelated genes. The specification also provides guidance for general methods of detecting polymorphisms (pg. 17-18). HOWEVER, the specification does not provide guidance as to how to determine disorder-associated polymorphisms of the genes listed in a) through e) (of claim 39), wherein the occurrence of said polymorphisms is an indication that a greater dose of an anti-oxidant composition should be administered to a human.

3) No working examples are presented.

4) The invention is directed to methods of selecting a dose of an anti-oxidant composition for administration to a human, comprising assessing occurrence in the human's genome of disorder-associated polymorphisms in at least two genes selected from the group consisting of

a) genes which encode an enzyme that catalyzes conversion of a toxic oxygen species to a less toxic oxygen species;

b) genes which encode a protein that provides protection against oxidative stress;

c) genes which encode a protein that induces production of a toxic oxygen species;

d) genes which encode a protein that indirectly affects oxidative stress; and

e) genes which encode a protein which the level of expression of the protein is associated oxidative stress, whereby the occurrence of any of the polymorphisms is an indication that a greater dose of the composition should be administered to the human; and selecting a dose of the composition based on occurrence of the polymorphisms.

5) The prior art of Forsberg et al. (Arch. Biochem Biophys (2001) May 1: 389(1): 84-93) teaches a detailed review of polymorphisms and oxidative stress. Specifically, Forsberg teaches polymorphisms in several genes related to oxidative stress and their effects (Table I and pgs. 85-89). Forsberg also teaches that while actually finding polymorphisms is not unduly burdensome (pg. 84, 2nd column), determining the actual phenotypic effect (i.e. correlating the polymorphism to a condition), requires extensive studies (pg. 85, 1st column).

Forsberg states,

"*These are the early days for using a genetic epidemiological approach to the study of oxidative stress-related disease.* As has been the case for other association studies, *it is expected that positive studies will be contrasted by negative results.* Therefore, *large-scale genotyping methods and carefully selected populations will be required to generate reliable data...to determine the impact of oxidative stress*...Human genome and comprehensive polymorphisms data will become available shortly, determination of phenotypes will proceed more slowly, but eventually a global approach where many carefully characterized genetic variants will be queried in disease association studies is an achievable goal" (pg. 90, 2nd column to pg. 91, 1st column).

In summary, Forsberg underscores the difficulty and unpredictability in the art, of correlating polymorphisms and oxidative stress.

6) The level of skill in molecular biology is high.

7) The results of experiments involving correlating polymorphisms and oxidative stress are not predictable, as taught above by Forsberg.

8) The claims are broadly drawn, reciting any possible polymorphism in any number of genes.

Based on the above analysis, one of ordinary skill in the art would be subject to undue experimentation in carrying out the method as claimed. Accordingly, the specification has not adequately taught of one ordinary skill in the art how to practice the claimed invention.

Conclusion

7. No claims area allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
November 25, 2002

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

11/26/02